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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/078,278	02/20/2002	Robert E. Wagner JR.	007274-01	3427
36234 7590 01/18/2007 JENNIFER M MCCALLUM, PH D, ESQ THE MCCALLUM LAW FIRM, LLC 685 BRIGGS STREET PO BOX 929 ERIE, CO 80516			EXAMINER BAUSCH, SARAE L	
			ART UNIT 1634	PAPER NUMBER
			MAIL DATE 01/18/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action  
Before the Filing of an Appeal Brief**

Application No.

10/419,935

Applicant(s)

LOU ET AL.

Examiner

Sarae Bausch

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**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 13 November 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires \_\_\_\_\_ months from the mailing date of the final rejection.  
b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**NOTICE OF APPEAL**

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

**AMENDMENTS**

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
(a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);  
(b) ☒ They raise the issue of new matter (see NOTE below);  
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: see continuation. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
5. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.  
6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
The status of the claim(s) is (or will be) as follows:  
Claim(s) allowed: none.  
Claim(s) objected to: \_\_\_\_\_.  
Claim(s) rejected: 1-18, 29-31 and 34-37.  
Claim(s) withdrawn from consideration: 19-28, 32 and 33.

**AFFIDAVIT OR OTHER EVIDENCE**

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

**REQUEST FOR RECONSIDERATION/OTHER**

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see continuation.  
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_.  
13. ☐ Other: \_\_\_\_\_.

### CONTINUATION

1. The response filed on 12/26/2006 is not found persuasive and the final office action, mailed 07/26/2006 has been maintained.
2. With regard to the applicants arguments directed to the rejections under 35 U.S.C. 112(1), all arguments have been thoroughly reviewed but not found persuasive. The response points to numbered paragraphs within the specification for support for the claimed subject matter. However the specification submitted on 02/20/2002 does not contain paragraph numbers and upon review of the pgpub, US2004/0224336A1 there appears no reference of the cited paragraph numbers for support of the claims. Therefore, it is unclear where in the specification applicant is relying upon for support for the claimed invention.

With regard to applicants arguments that the specification does teach that one or more components must be labeled and that subsequent detection is dependent on "co-localization" of two or more components, it is noted that the specification teaches, at most, simultaneous detection of three labels (see page 19, lines 5-10). The specification does not disclose more than three labels detected simultaneously nor does the specification teach co-localization of two or more components. The claims broadly encompass positive signal detection of more than two components, which encompasses 4, 5, 6, etc components detected by a positive signal upon co-localization and the specification does not teach nor describe more than three components detected simultaneously. Furthermore, the claims encompass detecting a positive signal only when two or more components are co-localized and the specification does not teach detection of a positive signal with two or more components are co-localized. The specification only describes simultaneous detection of two (or three) labels (see page 19, lines 5-10) and does not

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teach that detection of a label is a positive signal. Therefore, the specification does not teach co-localization of two "or more" components nor teach that a positive signal is generated "only" when two or more components are co-localized.

3. With regard to the applicants arguments directed to the rejections under 35 U.S.C. 103(a), all arguments have been thoroughly considered and not found persuasive.

The response that Kigawa teaches the use of RecA for determining the presence of large scale chromosomal type mutations and teaches the use of probes with at least 90 to 95% homology with the target nucleic acid. The response asserts that one of ordinary skill in the art would appreciate that such homology levels would not allow for detection of SNPs, insertions or deletions of the present invention. The response further asserts that Kigawa does not provide any motivation for a person of ordinary skill in the art to use MutS. This response has been thoroughly reviewed but not found persuasive.

Kigawa et al. teach detection of chromosomal aberrations such as deletion and insertions and teach the probes are *at least* 90 to 95% homologous to the target nucleic acid, which does not teach determining the presence of large-scale chromosomal type mutations (see column 6, lines 11-15 and column 12, lines 18-22). Furthermore, Kigawa et al. teach detection of specific genes (see column 12, lines 6-17) which is contrary to applicants assertion that Kigawa et al. teaches the use of RecA for determining the presence of large scale chromosomal type mutations. The reference is silent with regard to the size of the deletion and insertions that are detected within the chromosome. Furthermore, Kigawa et al. teaches the use of additional single stranded binding proteins to accelerate the reaction (see column 9, lines 18-22) which provides

motivation for one of skill in the art to use additional components, more specification single stranded binding proteins to accelerate the reaction and MutS is a single stranded binding protein.

The response asserts that Nolan teaches the use of MutS for determination of small errors in single stranded DNA and does not teach labeling the MutS. It is noted that Nolan teaches the use of MutS for SNP detection (see page 5, lines 14-22 and figure 1). Therefore Nolan does not teach the use of MutS for determination of small errors in single stranded DNA but does teach the use of MutS for detection of SNP analysis. Furthermore, Nolan et al. teach MutS bound to microspheres containing affinity tag binding partners and therefore teach a labeled MutS, wherein MutS is labeled with a microspheres as well as an affinity tag (see page 5, lines 23-29).. The claims are not limited to a specific label or position of a label on MutS.

The response asserts that there was no reasonable expectation of success that MutS would bind a triple helix structure and assert that the cited patent that teaches that MutS does bind triple helix formations teaches away from the MutS binding triplex DNA structures. The response asserts that US Patent 6120992 teaches that triplex helix structures require one non-DNA strand for binding to occur and therefore the reference provides no suggestion to binding MutS to DNA triplex structures. This response has been thoroughly reviewed but not found persuasive. '992 teaches the breadth of the ability of MutS to work with multiple different triplex formations and does not teach that it is required that one of the strands of the triplex formation must be PNA. '992 does not teach the limitation but demonstrates the breadth of the ability of MutS to bind different triplex and duplex structures. One of ordinary skill in the art would expect that MutS would bind not only the various triplex formations comprising DNA, RNA and PNA as taught in

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'662 but also DNA triplexes without DNA analogues. There is no teaching in '662 that MutS cannot bind a DNA triplex and therefore there is a reasonable expectation of success that MutS would bind triplex structures.

The response asserts that MutS has no interaction with RecA during repair or replication errors and asserts the function of MutS is to repair replication errors whereas RecA is a recombination protein. The response further asserts that RecA and MutS are very different to the action of both agents. The response asserts that the examiner points to no teaching in the art that suggest such systems would work with such unnatural structures. This response has been thoroughly reviewed but not found persuasive. It is noted that the examiner did not assert that RecA and MutS interact during repair or replication, but that both proteins are components or part of the mismatch repair system for E.Coli with no assertion that the proteins interact. Furthermore, it is noted that the examiner is not asserting that RecA and MutS function the same in vivo and in vitro, however based on the teaching in the prior art, one of ordinary skill in the art would have been motivated to use MutS with RecA for detection of mutations as '992 teaches that MutS binds triplexes, Kigawa teaches the use of single stranded binding proteins accelerate the RecA triplex formation and detection of chromosomal deletions and insertions coupled with Nolan teach the use of MutS to detection SNPs, which are encompassed by chromosomal deletions and insertions. Therefore, based on the teachings of Kigawa in view of Nolan, coupled with the evidence in the art with the teaching that MutS binds a triplex, one of skill in the art would have been motivated to use MutS with RecA to detection deletions, insertions, and SNP in a target nucleic acid.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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